REMARKS

Claims 29-33, 39-42 and 52 are pending. Claims 29-31, 40-42 and 52 have been amended, and claims 33 and 39 have been canceled without prejudice.

Claims 29-33, 39-42 and 52 were rejected under 35 U.S.C. 112, first paragraph. The specification has been objected to for failing to provide literal support for "a cell-free cartilage membrane."

While Applicants fully disagree with the rejection, the term "cell-free" has been deleted from the claims. Withdrawal of the rejection is therefore requested.

All the remaining rejections are made under 35 U.S.C. § 102. For reasons discussed below, each of these rejections are properly withdrawn. See, for instance, *In re Marshall*, 198 USPQ at 346 ("rejections under 35 USC 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art.").

Claims 29-33 and 52 are rejected under 35 U.S.C. § 102 (b) as being anticipated by U.S. Patent No.5,759,190 (Vibe-Hansen). The Office Action asserts that Vibe-Hansen discloses a cartilage membrane comprising at least one surface part carrying a composition comprising at least one stimulation molecule which induces signal transduction in chondroblast/chondrocytes and which is selected from collagen proteins, proteoglycans and non-collagenous proteins.

Applicants respectfully traverse the rejection. The present invention provides a membrane suitable for use when e.g. chondrocytes are transplanted into a cartilage defect to repair the defect. A membrane as claimed contains specific molecules that stimulate signal transduction in the transplanted chondrocytes whereby hyalin cartilage is formed.

In contrast, Vibe-Hansen relates to transplantation of chondrocytes and describes two different membranes, namely i) a hemostatic barrier serving to block vascular invasion of the cartilage site to be repaired (column 3, line 35-37) and ii) a cell-free barrier which isolates the repair site and keeps **transplanted** cells **in place** (column 3, line 35-39). To fix the membranes **in place,** Tisseel® was used. Tisseel® is an organic glue that is based on a reaction between clotting proteins (e.g. fibrinogen) and thrombin. When fibrinogen and thrombin react, fibrin is formed as a clot. The Tisseel® employed by Vibe-Hansen et al. is as described in column 5, *i.e.*

> *"The Tisseel® kit consists of the following components:*
> *Tisseel®, a lyophilized, virus-inactivated Sealer, containing clottable protein, thereof fibrinogen, Plamafibronection (CIC) and Factor NU and Plasminogen.*
> *Aprotenin Solution (bovine)*
> *Thrombin 4 (bovine)*
> *Thrombin 500 (bovine)*
> *Calcium Chloride solution*
> *... The fibrin adhesive or the two-component sealant using Tisseel® kit is combined in the manner according to Immuno AG product insert sheet."*

As evident from the data sheets enclosed as Exhibit A, Tisseel® is a two-component sealant, the one component being clottable protein and calcium chloride, and the other component being thrombin and aprotenin. Accordingly, the application of Tisseel® on a hemostatic membrane or a cell-free barrier as described in Vibe-Hansen et al. **results in formation of a sealant**, i.e. the clottable protein like fibrinogen has reacted with thrombin to form a fibrin clot. Accordingly, the clottable protein like e.g. fibrinogen as such is not present on the membrane or barrier as it has reacted with thrombin to form long chain of fibrin molecules known as fibrin aggregates or fibrin polymer. Rather, a new macro-molecule has been formed by covalent bondings and this molecules is now different from fibrinogen.

In contrast hereto, a stimulation molecule like e.g. fibrinogen is used in an **unreacted** form in accordance with the present invention.

Moreover, as shown in the paper by Brittberg et al. (Biomaterials, vol. 18 (3) (1997), pp 235-242 – previously filed) Tisseel® impairs the natural repair of the osteochondral defect and, accordingly, Tisseel® cannot have any capacity of inducing signal transduction in chondrocytes resulting in formation of hyalin cartilage. Although Tisseel® contains e.g. fibrinogen, which in the present application is used as a stimulation molecule due to its properties in the present context, the fibrinogen in Tisseel® is reacted with thrombin to form fibrin aggregates, i.e. one or two peptides have been removed by means of thrombin (cf. Merck index 4103 relating to fibrin) and covalent bondings have been established.

Due to the fact that clottable protein like e.g. fibrinogen as such is not present in the membrane or barrier described by Vibe-Hansen et al. and the fact that Tisseel® has been found to impair the natural repair of an osteochondral defect, the proteins in Tisseel® **cannot be stimulation molecules** as claimed herein in the present invention.

Additionally, independent claim 29 has been amended to incorporate features of former claim 39, which former claim was not rejected over Vibe-Hansen.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 29, 31, 32, and 52 are rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent No. 5,876,452 (Athanasiou). The Office Action asserts that Athanasiou discloses a cell-free cartilage membrane (implant) and kit comprising at least one surface part carrying a composition comprising at least one stimulation molecule, which is selected from collagen proteins, proteoglycans and non-collagenous proteins.

Applicants traverse the rejection. Athanasiou does not describe a "cartilage membrane, comprising at least one surface part carrying a composition comprising at least one stimulation molecule, which i) comprises at least one RGD motif; ii) is selected from the group consisting of

collagen proteins, proteoglycans, and non-collageneous proteins, wherein the collagen protein is selected from the group consisting of collagen type II, VI, IX and XI; and iii) induces a signal transduction in chondroblasts/chondrocytes resulting in chondroblasts/chondrocytes producing and secreting matrix components that form hyalin cartilage, the cartilage membrane being a natural or synthetic collagen type I membrane or part thereof." Athanasiou nowhere teaches the claimed invention.

Additionally, independent claim 29 has been amended to incorporate features of former claim 39, which former claim was not rejected over Athanasiou.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 29, 31-33, and 52 are rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent No. 6,080,194 (Pechence). The Office Action incorrectly asserts that Pachence discloses a cell free cartilage membrane and kit comprising at least one surface part carrying a composition comprising at least one stimulation molecule. The rejection is traversed.

Pachene relates to a collagen membrane and a collagen matrix made of collagen I (see Example 1 and 2). However, collagen I is not included in the definition of a stimulation molecule in the sense of the present invention, cf. the amended claim 29. For instance, Type I Collagen is the major component in tissues like bone and connective tissue but is not present in hyaline cartilage. Furthermore, type I collagen is highly present in fibrocartilage, and expressed in increased amount in OA chondrocytes (Lorenz H., Arthritis Res., 2005; Shibakawa A., Osteoarthritis and Cartilage, 2003). This emphasizes that type I collagen is not a stimulation molecule for chondrogenesis and expression of hyaline cartilage.

Pachene does not describe a membrane as claimed in the present invention.

Indeed, independent claim 29 has been amended to incorporate features of former claim 39, which former claim was not rejected over Pachene.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 29-33, 39-42, and 52 are rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent No. 6,251,143 (Schwartz). The Office Action asserts that Schwartz discloses a membrane having an attachment factor and/or cell cartilage membrane and kit comprising at least one surface part carrying a composition comprising at least one stimulation molecule. The rejection is traversed.

Schwartz reports a certain insert that is made of a bioabsorbable material, which may include a repair factor or attachment factor that is releasably disposed in the insert (column 4, lines 16-31).

The insert of Schwartz et al. is not a membrane as Applicants disclose and claim. In column 3, lines 37-40 of Schwartz et al. it is mentioned that the insert may be a flexible porous film consisting essentially of completely bioabsorbable material. However, there is no reference or indication that such a film firstly should be a natural or synthetic collagen type I membrane or part thereof as claimed in the present invention and secondly, there is no indication that such a film contains a stimulation molecule. On the contrary, the skilled worker would understand that the film only contains the film-forming material. Thirdly, in column 10 of Schwartz et al. is mentioned a number of different materials that are said to be suitable to use as bio-absorbable materials *for* the insert. Such materials include:

> *"hyaluronic acid (e.g. as a fiber matrix), polyglycolic acid (e.g. as fiber matrix), collagen, including type I collagen (e.g. as a sponge matrix), polylactic acid (e.g. as a fiber matrix), fibrin clot (which can be filled and molded into the delivery unit), collagen gel (which can be overlayed into a polyglycolic acid matrix), polydioxane, polyester, alginate or combinations thereof"*

In other words, *there* is no indication that the insert in the form of a film mentioned in column 3 should he made of collagen type I as the collagen is used to form a sponge matrix. Accordingly, Applicants request withdrawal of the rejection and allowance of the claims.

Claims 29-33, 39-42, and 52 are rejected under 35 U.S.C. § 102 (b) as being anticipated by U.S. Patent No. 5,236,447 (Kubo). The rejection is traversed.

Kubo et al relates to woven fabrics and not to a membrane that is a natural or synthetic collagen type I membrane or part thereof. Accordingly, Kubo does not anticipate the present invention. Accordingly, Applicants request withdrawal of the rejection and allowance of the claims.

Claims 29-33, 39-42, and 52 are rejected under 35 U.S.C. § 102 (b) as being anticipated by U.S. Patent No. 5,236,447 (Li). The rejection is traversed.

Li relates to a method for the preparation of a dense collagen membrane especially for use in the oral cavity in connection with periodontal lesions. In column 6, lines 59-70 it is said that the dispersion of collagen used in the claimed method may contain additives, Among others are mentioned glycoproteins such as fibronectin. However, addition of e.g. fibronectin to the dispersion will not result in a membrane containing fibronectin as such due to the fact that the dispersion in a subsequent step is subjected to a cross-linking step involving the use of e.g. formaldehyde or glutaraldehyde (see column 8, lines 18-44). Such a treatment will introduce multiple covalent bondings and change the overall protein structure, function and amino acid sequence related to fibronectin and, accordingly, if fibronectin should have been included in the collagen dispersion, the resulting membrane does not contain any fibronectin, but a crosslinked polypeptide sequence with no secondary or tertiary structures needed for biological activity. Furthermore, the polypeptide will no longer contain any ROD sequence but a chemical derivation thereof. Accordingly, a membrane according to Li does not contain any stimulation

molecule in the sense of the present invention. Accordingly, Applicants request withdrawal of the rejection and allowance of the claims.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

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Stephana E. Patton (Reg. No. 50,373)
Peter F. Corless (Reg. No. 33,860)
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
Telephone: 617-439-4444
Facsimile: 617-439-4170

Customer No.: 21874

EXHIBIT A

THE MERCK INDEX

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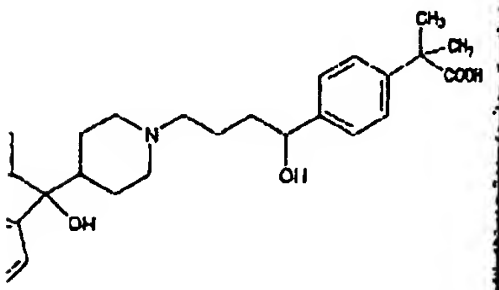
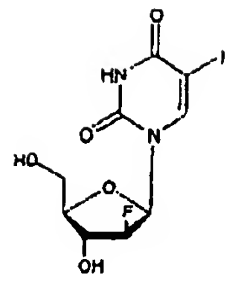
is include sesquiterpene lactones such as parthenol. J. Hylands, D. M. Hylands in *Developments in Drug Medicines*, J. W. Gorrod *et al.*, Eds. (Ellis Horchester, 1986) pp 103-104. Inhibition of prostaglanthesis by feverfew extract: H. O. J. Collier *et al.*, 922 (1980). Effect on human platelet phospholipase heja, J. M. Bailey, *ibid.* 1054 (1981), *eidem*, *Prog. Leukotrienes Med.* 8, 653 (1982); J. K. Thakkar *et al. Biophys. Acta* 750, 134 (1983). Inhibition of platelry activity: S. Heptinstall *et al.*, *Lancet* 1, 1071 Heptinstall *et al.*, *J. Pharm. Pharmacol.* 39, 459 ructure and anti-secretory activity study: W. A. Groet al., *ibid.* 38, 709 (1986). Clinical trials in migraine dried feverfew leaves: E. S. Johnson *et al.*, *Brit.* 1, 569 (1985). Use of oil extract in migraine: K. S. al., US 4788433 (1988 to R. P. Scherer). *Review*, *Pharm. J.* 232, 611-614 (1984). Brief review of possible side effects: C. A. Baldwin *et al.*, *ibid.* 38 (1987).

Fexofenadine. [83799-24-0] α,α-Dimethyl-4[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]etic acid; carboxyterfenadine; terfenadine carboxylic 16455. $C_{32}H_{39}NO_4$; mol wt 501.65. C 76.62%, H 2.79%, O 12.76%. Nonsedating-type histamine H_1 antagonist. Prepn: A.A. Carr *et al.*, DE 3007876; 4254129 (1980, 1981 both to Richardson-Merrell) on as active metabolite of terfenadine, *q.v.*: D. A. al., *Arzneimittel-Forsch.* 32, 1185 (1982). Synthesis al *et al.*, *J. Org. Chem.* 59, 2620 (1994). HPLC assay n terfenadine: K. Y. Chan *et al.*, *J. Chromatog.* 571,): determn in biological fluids: A. Terheerhte, G. Bas A 694, 219 (1995). Effects on cardiac K^+ channels *et al.*, *Mol. Pharmacol.* 44, 1240 (1993). Comparis of cardiotoxic potential: J. A. Hey *et al.*, *Arzneisch.* 46, 153 (1996). Clinical pharmacology in chil. R. Simons *et al.*, *J. Allergy Clin. Immunol.* 98, 169



; from methanol-butanone, mp 195-197° (Carr); als white crystals from methanol, mp 142-143° (Kaura hloride. [153439-40-8] Allegra; Telfast. $C_{32}H_{39}$ mol wt 538.13.
CAT: Antihistaminic.

Fialuridine. [69123-98-4] 1-(2-Deoxy-2-fluoro-β-D-furanosyl)-5-iodo-2,4(1*H*,3*H*)-pyrimidinedione; 1-(2-fluoro-β-D-arabinofuranosyl)-5-iodouracil, 5-iodo-2′-deoxyuracil; FIAU. $C_9H_{10}FIN_2O_5$; mol wt 372.09. C 29.05%, H 2.71%, F 5.11%, I 34.11%, N 7.53%, O 21.50%. Viral agent; nucleoxide analog with antihepadnavirus prepn: K. A. Watanabe *et al.*, *J. Med. Chem.* 32, 2 Antiviral activity: J. M. Colacino, C. Lopez, *Antimicrob. Chemother.* 24, 505 (1989); K. A. Stanchfield *et al.*, *Antivir. Res.* 23, 45 (1994). Clinical pharmacokinetics: R. *et al.*, *Antimicrob. Ag. Chemother.* 38, 2131 (1994). trial suspension: S. R. Ahmed, *Lancet* 343, 1 evaluation of mechanism of hepatotoxicity: L. Cui, *Invest.* 95, 535 (1995). Clinical toxicological profile nson *et al.*, *Transpl. Proc.* 27, 1219 (1995).



Crystals from ethanol, mp 216-217°.

4103. Fibrin. [9001-31-4] Fibrin monomer is fibrinogen from which one or two peptides have been removed by means of thrombin: Laki, Chandrasekhar, *Nature* 197, 1267 (1963). The term fibrin is usually applied to polymerized fibrin monomer. Terminal clotting takes place in four steps: (1) fibrinogen hydrolyzes under the influence of thrombin into fibrin and fibrinopeptide fragments; (2) fibrin forms soft clots which can be readily dispersed; (3) thrombin activates fibrin-stabilizing factor, *q.v.*, an enzyme precursor, present in blood plasma; (4) fibrin in the networks cross-links under the influence of the activated FSF to give the final hard clots: *Chem. & Eng. News* 43, no. 32, 38 (1965); O. D. Ratnoff, H. Bennett, *Science* 179, 1291 (1973). Fibrin occurs in two principal forms, *fibrin-I*, "insoluble" fibrin, differing from *fibrin-S*, "soluble" fibrin, by urea solubility as well as other characteristics. Fibrin-I is formed through the reaction of a fibrinogen-like plasma protein, FSF, which in the presence of Ca^{2+} converts what would otherwise be a "soluble" weakly bonded gel into a covalently bonded, insol clot: Rosenberg, Carman, *Nature* 204, 994 (1964). Chemical nature of crosslinking segments: Chen, Doolittle, *Proc. Nat. Acad. Sci. USA* 66, 172 (1970); *eidem*, *Biochemistry* 10, 4486 (1971); Doolittle *et al.*, *Biochem. Biophys. Res. Commun.* 44, 94 (1971). *Reviews:* W. H. Seegers, *Prothrombin* (Harvard University Press, 1962) 728 pp; Laki, Gladner, *Physiol. Rev.* 44, 127 (1964); Lorand, *Fed. Proc.* 24, no. 4, part 1, 784 (1965); A. L. Copley, *Thromb. Res.* 14, 249 (1979). Review of chemistry: several authors, *Thromb. Diath. Haemorrh., Suppl.* 39 (1970).

4104. Fibrinogen. [9001-32-5] Factor I; Parenogen. A plasma glycoprotein belonging structurally to the keratin-myosin group. Synthesized and secreted by hepatic parenchymal cells. Present to the extent of 0.3-0.4 g/100 ml in human plasma. Essential to the clotting of blood. Its synthesis is greatly increased during acute inflammatory challenge. The fibrinogen molecule consists of three peptide chains, α (A), β (B), and γ (C), crosslinked by several disulfide bonds. The mol wt of about 400,000 represents a dimeric form of the molecule. Thrombin releases fibrinopeptides A and B from the *N*-terminal ends of the α and β chains of fibrinogen in the formation of fibrin during coagulation. Because fibrinogen is less sol than other plasma proteins it is readily separated by precipitation with sodium chloride: Florkin, *J. Biol. Chem.* 87, 629 (1930); or with ammonium sulfate: Nanninga, *Arch. Neer. Physiol.* 28, 241 (1946). Prepn from human plasma: Edsall *et al.*, *J. Am. Chem. Soc.* 69, 2731 (1947). Purification: Cama *et al.*, *Naturwiss.* 48, 374 (1961). End group determination: Lorand, Middlebrook, *Science* 118, 515 (1953). Sinnamic studies: Schauenstein, Hochegger, *Z. Naturforsch.* 8b, 473 (1953); Edsall, *J. Polymer Sci.* 12, 253 (1954). *Reviews:* Seegers, *Physiol. Rev.* 34, 711 (1954); Lorand, *Fed. Proc.* 24, no. 4, part 1, 784 (1965); several authors, *Thromb. Diath. Haemorrh., Suppl.* 39 (1970); A. L. Copley, *Thromb. Res.* 14, 249 (1979). Fibrinogen has been shown to be the receptor for the endogenous lectin (agglutinin) secreted by activated platelets: T. K. Gartner *et al.*, *Nature* 289, 688 (1981). Review of biosynthesis: G. M. Fuller, D. G. Ritchie, *Ann. N.Y. Acad. Sci.* 389, 308-322 (1982).
Sparingly sol in water. Aq solns are viscous. Isoelectric point 5.5. Readily denatured by heating to 56° or higher, and by chemical agents such as salicylaldehyde, naphthoquinone sulfonates, ninhydrin, and alloxan. Small amounts of papain will clot fibrinogen, but larger amounts will digest the clot.
THERAP CAT: Coagulant (clotting factor).

4105. Fibroblast Growth Factor. [62031-54-3] FGF. Growth stimulatory factor originally isolated from bovine brain and pituitary and found to stimulate DNA synthesis in cultured fibroblast cells. Isoln: D. Gospodarowicz, *Nature* 249, 123 (1974). Mitogenic effect on cultured cell lines and induction of amphibian limb regeneration *in vivo*: D. Gospodarowicz *et al.*, *Advan. Metab. Disord.* 8, 301 (1975). Two closely related forms have been identified, known as basic (*bFGF*) and acidic (*aFGF*) fibroblast growth factors, having a total amino acid sequence homology of 55%. Both induce the proliferation and differentiation of a wide variety of cell types, including corneal and vascular endothelial cells, myoblasts, chondrocytes, osteoblasts and glial cells. FGF has neurotrophic and angiogenic activity and may play an important role in the wound healing process. Purification of bFGF from pituitary: D. Gospodarowicz, *J. Biol. Chem.* 250, 2515 (1975); from brain: D. Gospodarowicz *et al.*, *ibid.* 253, 3736 (1978). Identification of aFGF from bovine brain: K. A. Thomas *et al.*, *ibid.* 255, 5517 (1980). Comparison of fibroblast growth factors: S. K. Lemmon *et al.*, *J. Cell Biol.* 95, 162 (1982). Purification and characterization of bFGF: K. A. Thomas *et al.*, *Proc. Nat. Acad. Sci. USA* 81, 357 (1984). Identity of bFGF from brain and pituitary: D. Gospodarowicz *et al.*, *ibid.* 6963. Amino acid sequence of bFGF: F. Esch *et al.*, *ibid.* 82, 6507 (1985); of aFGF: G. Gimenez-Gallego *et al.*, *Science* 230, 1385 (1985); F. Esch *et al.*, *Biochem. Biophys. Res. Commun.* 133, 554 (1985). Possible identity of aFGF with *endothelial cell growth factor* (*ECGF*) and *eye-derived growth factor-II* (*EDGF-II*): A. B. Schreiber *et al.*, *J. Cell Biol.* 101, 1623 (1985); of bFGF with *macrophage-derived growth factor* (*MDGF*): A. Baird *et al.*, *Biochem. Biophys. Res. Commun.* 126, 358 (1985); of FGFs with *retina-derived endothelial cell growth factors*: A. Baird *et al.*, *Biochemistry* 24, 7855 (1985). Cloning of cDNA for bovine bFGF: J. A. Abraham *et al.*, *Science* 233, 545 (1986); for human bFGF: T. Kurokawa *et al.*, *FEBS Letters* 213, 189 (1987); M. Iwane *et al.*, *Biochem. Biophys. Res. Commun.* 146, 470 (1987). Expression of a chemically synthesized gene for bioactive bovine aFGF: D. L. Linemeyer *et al.*, *Biotechnology* 5, 960 (1987). Receptor binding study: G. Neufeld, D. Gospodarowicz, *J. Biol. Chem.* 261, 5631 (1986). FGF-like factors have been isolated from several human tumor cell lines: R. R. Lobb *et al.*, *Biochem. Biophys. Res. Commun.* 139, 861 (1986); M. Klagsbrun *et al.*, *Proc. Nat. Acad. Sci. USA* 83, 2448 (1986); D. Moscatelli *et al.*, *J. Cell. Physiol.* 129, 273 (1986). FGF has also been shown to be structurally homologous to the protein products of several oncogenes: C. Dickson, G. Peters, *Nature* 326, 833 (1987); M. Taira *et al.*, *Proc. Nat. Acad. Sci. USA* 84, 2980 (1987); P. Dell'Era Bovi *et al.*, *Cell* 50, 729 (1987). Review of tissue distribution and bioactivity of bFGF: A. Baird *et al.*, *Rec. Prog. Horm. Res.* 42, 143-205 (1986). Review of structural characterization and biological functions: D. Gospodarowicz *et al.*, *Endocrine Rev.* 8, 95-114 (1987). Potential role in the control of pituitary and gonad development: D. Gospodarowicz, N. Ferrara, *J. Steroid Biochem.* 32, 183-191 (1989). *Reviews:* K. A. Thomas, G. Gimenez-Gallego, *Trends Biochem. Sci.* 11, 81-84 (1986); D. Gospodarowicz *et al.*, *Mol. Cell. Endocrinol.* 46, 187-204 (1986); K. A. Thomas, *FASEB J.* 1, 434-440 (1987).

Acidic fibroblast growth factor. [106096-92-8] pI 5-7. Exists in 2 microheterogeneous forms: *aFGF-1*, a 140 amino acid peptide, mol wt 15,900 daltons, and *aFGF-2*, an amino truncated form lacking 6 amino terminal residues, mol wt 15,200 daltons.

Basic fibroblast growth factor. [106096-93-9] pI 9.6. 146 amino acid peptide, mol wt ~16,000 daltons. Also exists as an amino truncated form, *des 1-15 bFGF*, lacking the first 15 amino acid residues.

4106. Fibroin. [9007-76-5] Protein filaments produced by members of the phylum *Arthropoda*, particularly by certain species belonging to the classes *Insecta* (insects) and *Arachnida* (spiders, etc.). Fibroin is the main protein of silk and is secreted